Section II (Remarks)

A. Response to Objection Regarding 37 C.F.R. 1.97, 1.98 and MPEP § 609

On page 2 of the Final Office Action of October 18, 2007, the examiner objected to the missing publication date of reference "AY," which is a German patent application and is listed as foreign patent document DE 199 33 492 A1 on the Information Disclosure Statement filed July 20, 2007. The examiner cited the missing publication date as failure to comply with the provisions of 37 C.F.R. §§ 1.97, 1.98 and MPEP § 609, and under 37 C.F.R. § 1.97(i), included DE 199 33 492 A1 in the file history but did not consider the reference as to its merits.

The examiner's attention is respectfully drawn to the second sentence of 37 C.F.R. § 1.97 (f) which states in pertinent part, "if a bona fide attempt is made to comply with § 1.98, but part of the required content is inadvertently omitted, additional time may be given to enable full compliance." The publication date of DE 199 33 492 A1, which was inadvertently omitted and is printed on the face of the document, is January 18, 2001.

Additionally, foreign patent document WO – 01/05432 A2, published on January 25, 2001, and also listed on the Information Disclosure Statement filed on July 20, 2007, is the PCT application corresponding to German patent application DE 199 33 492 A1. The information disclosed in PCT application WO01/05432 A2, already considered by the examiner on the merits, includes the entire disclosure of German patent application DE 199 33 492 A1. Therefore, since the information in DE 199 33 492 A1 has already been made of record and was considered by the examiner, the applicant has satisfied the duty of disclosure required under 37 C.F.R. § 1.56 and is under no continuing obligation to resubmit German patent application DE 199 33 492 A1.

37 C.F.R. § 1.56 (a) states, in pertinent part that, "the duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98." WO01/05432 A2 was submitted in the manner prescribed by §§ 1.97(b)-(d) and 1.98, and the substance of DE 199 33 492 A1 is included within WO01/05432 A1, so that this objection is moot. For the foregoing reasons, the applicant respectfully requests the examiner to withdraw this objection.

B. Amendments to the Claims

By the present Amendment, claim 20 is amended, claims 1-3, 5, 6, 8-19, and 28 have been canceled, and no new claims have been added. Claims 4 and 7 were previously canceled. No new matter within the meaning of 35 U.S.C. §132 has been introduced by the amendment to claim 20.

The amendment to claim 20 deletes the inadvertent duplication of the word "protein" at the end of the phrase "a phage-holin protein," and also deletes "or a defensin" which follows the aforementioned phrase. The deletion of the recital of "defensin" does not add new matter and is fully consistent with and supported by the originally-filed disclosure of this application.

Thus, upon entry of the amendments, claims 20-27, 29 and 30 are pending.

C. Rejection of Claims 1-3, 5, 6, 8-14 and 18-30 under 35 U.S.C. § 103 (a)

Claims 1-3, 5, 6, 8-14, and 18-30 were rejected under 35 U.S.C. §103(a) in the October 18, 2007 Office Action, as being unpatentable over Nielsen et al. (US 6,548,651), Good et al. (Nature Biotechnology, Vol. 19:360-364, 4/2001; hereinafter "Good et al.") and Rothbard et al. (WO 98/52614; hereinafter "Rothbard et al."), in view of Saido-Sakanaka et al. (Biochem. J. Vol. 338:29-33, 1999; hereinafter "Saido-Sakanaka et al.") and Yu et al. (cited in Applicants' October 14, 2004 IDS; hereinafter "Yu et al."), Good et al. (Nature Biotechnology, Vol. 16:355-358; hereinafter "Good et al. (2)") and Braun et al. (U.S. 6,821,948; hereinafter "Braun et al.").

It is elemental law that in order for an invention to be obvious, the difference between the subject matter of the application and the prior art must be such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art. In order to meet this standard for a proper §103 rejection, all claim limitations must be disclosed or derivable from the cited combination of references, and there must be a logical reason to combine the cited references to produce an operable combination. See MPEP §2143:

> **"2143 Basic Requirements of a Prima Facie Case of Obviousness**
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> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art,

> to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
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> "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

The cancellation of claims 1-3, 5, 6, 8-19, and 28, in addition to the amendment of claim 20 removes defensin peptides from the claimed transport mediators. The claimed invention is directed to a conjugate suited for treatment of prokaryotic infections, comprising a peptide nucleic acid (PNA) directed against the deoxyribonucleic acid (DNA) of a gene giving antibiotic resistance, in order to resensitize the bacteria to an antibiotic against which the bacteria was previously resistant. Specifically, the claims recite a conjugate utilizing a phage-holin protein linked to a PNA to be introduced into the prokaryote and directed against the DNA of a gene giving antibiotic resistance, where the PNS inhibits the transcription of the gene.

Since none of the cited references describes the use of phage-holin proteins as transport mediators conjugated with a PNA to enable penetration of the prokaryotic cell membrane, the combination of cited prior art references do not teach or suggest all of the claim limitations and therefore a *prima facie* case of obviousness is not established.

On page 6, paragraph 2 of the October 18, 2007 Office Action the examiner relies on Saido-Sakanaka et al. and Yu et al. "to show that phage-holin and defensin polypeptides were know[n] at the time of the invention and were known to be antimicrobial cell membrane penetrating polypeptides." Neither Saido-Sakanaka et al. nor Yu et al. discloses phage-holin polypeptides.

Saido-Sakanaka et al. describes the synthesis and anti-bacterial activity of defensin polypeptides derived from a sequence of *A. dichotoma*. (Saido-Sakanaka et al., pg. 29, Abstract.) In order "[t]o determine the active site of defensin, we synthesized 64 overlapping 12-mer peptides spanning the sequence of defensin..." (Saido-Sakanaka et al., pg. 30, right column, 4th paragraph.) "[W]e looked for the active region of *A. dichotoma* defensin by measuring anti-bacterial activity against *S. aureus*." (Saido-Sakanaka et al., pg. 32, right column, 2nd paragraph.)

Saido-Sakanaka et al. identifies one defensin oligo-peptide sequence with high anti-bacterial activity and synthesizes analogs of that single peptide sequence to test for antibacterial activity and membrane permeability. (Saido-Sakanaka et al., pg. 31.) On page 31, right column, paragraphs one and two, and page 32 in the second paragraph of the discussion, Saido-Sakanaka et al. describes the differing results for membrane permeability and antibacterial activity of one isolated defensin oligo-peptide sequence and the synthesized analogs of that single defensin peptide sequence.

The examiner relies on Saido-Sakanaka et al. to show that phage-holin and defensive peptides "were known to be antimicrobial cell membrane penetrating polypeptides" which were well known in the art to be able to "form pores and penetrate cell membranes." (Final Office Action, pg. 6, paragraph 2.) There is no description of phage-holin polypeptides with these properties or any other disclosure of phage-holin polypeptides anywhere in Saido-Sakanaka et al.

In addition, on page 33, left column, paragraph 3, the state of the art of anti-bacterial peptides is summarized by Saido-Sakanaka et al. by the following, "[i]t has been suggested that ...anti-bacterial peptides permeate the cell membrane by forming an ion channel. However, recent studies on the mode of action of several anti-bacterial peptides showed that the peptides kill bacteria by a 'carpet-like' mechanism. The mechanism of anti-bacterial activity of the [defensin] fragment remains to be elucidated." There is no mention of phage-holin peptides in Saido-Sakanaka et al., and the disclosed testing of the defensin peptide for membrane permeability, as well as the uncertainty in regard to the mode of anti-bacterial action of the defensin polypeptide, fails to support the examiner's assertion that "phage-holin and defensin peptides were known in the art to be antimicrobial peptides that can form pores and penetrate cell membranes." Furthermore, since the anti-bacterial mode of action of the defensin peptides is disclosed not to involve penetration of the cell membrane (see above regarding the postulated "carpeting mechanism"), it would not have been obvious to one of the skill in the art "to choose any of the known bactericidal peptides known to permeate cell membranes" for use as a transport mediator, as alleged in the Final Office Action, at pg. 7, paragraph 1 thereof.

Yu et al. discloses the synthesis of a novel circularized structure of "β-tile peptide analogs of a typical rabbit alpha-defensin," and the antimicrobial activity of the cyclic defensin β-tile analogs at high salt concentration. (Yu et al. pg. 3943, Abstract, right column, paragraph 2.) There is no disclosure of the antibacterial activity of phage-holin polypeptides or discussion of phage-holin peptides as transport mediators in Yu et al. Additionally, although the antibacterial activity of the cyclic defensins is assayed in Yu et al., the mechanism of the anti-bacterial action of the cyclic defensins is not elucidated, i.e. Yu et al. does not anywhere disclose that the cyclic defensins penetrate the prokaryotic membrane, as is necessary for these peptides to operate as transport mediators. On page 3948, at paragraph 2, Yu et al. describes, "microbial killing by α-defensins has been attributed to the formation of multimeric pores on the on lipid surfaces. It remains to be seen if β-tile peptides and α-defensins act via similar mechanisms." Again, as in Saido-Sakanaka et al, Yu et al. provides no support for the examiner's assertion that "phage-holin and defensin peptides were known in the art to be antimicrobial peptides that can form pores and penetrate cell membranes." (Final Office Action, pg. 6, paragraph 2.)

Page-holin peptides are not described in Saido-Sakanaka et al. or Yu et al. and there is no teaching in either reference to use phage-holin peptides as transport mediators. In addition, both Saido-Sakanaka et al. and Yu et al. are wholly speculative about any mechanism of action of the anti-bacterial peptides. It therefore would not have been obvious to a person skilled in the art at the time of the invention to conjugate a phage-holin peptide as a transport mediator with a PNA targeting the DNA of a gene giving antibiotic resistance, and to arrive at the claimed conjugate, because the mechanism of action of the bactericidal peptides was unknown.

The examiner has asserted that Saido-Sakanaka et al. and Yu et al. demonstrate that phage-holin and defensin proteins were known in the art, and while these references disclose defensin peptides, there is no description of phage-holin peptides. In addition, none of the references cited by the examiner teach or indicate the use of phage-holin antibacterial peptides as transport mediators, or the conjugation of a phage-holin peptide with a PNA against a DNA of a gene giving antibiotic resistance, to arrive at the claimed conjugate for treating prokaryotic infections. Therefore, the combination of cited prior art references does not teach or suggest all of the claim limitations and a *prima facie* case of obviousness is not established. As such, the applicant

respectfully requests that the examiner withdraw the rejection of amended claim 20, claims 21 – 27, and claims 29 and 30.

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 20-27, 29 and 30 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance. If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

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